

DNA-TR-86-155.

THE PROLIFERATIVE CHARACTERISTICS OF INTESTINAL STEM CELLS

Response and Protection to High Energy or Fission Spectrum Neutrons or Photons

Wayne R. Hanson Rush-Presbyterian-St. Luke's Medical Center 1753 West Congress Parkway Chicago, IL 60612

30 April 1986

Technical Report



CONTRACT No. DNA 001-84-C-0061

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All other editions are obsolets.

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18. SUBJECT TERMS (Continued)

Fermilab High Energy Neutrons JANUS Fission Spectrum Neutrons

19. ABSTRACT (Continued)

than Ara/c. Results of this contrast showed that the combination of Ara/c and WR-2721 protected the gut from photon injury to a greater extent than each agent alone. The protection frc... Fermilab neutrons by the combination was slightly better than each agent and there was no additional protection of Ara/c combined with WR-2721 for injury by JANUS fission spectrum neutrons. These treatments did not alter the animal response at doses in the bone marrow lethal range. These data are consistent with findings that the intestinal clonogenic cell age distribution has less effect on high LET radiosensitivity. The results of experiments funded by this contract show that the intestinal stem cells are normally in a G scage of the cell cycle and respond to Ara/c by entering the cell cycle at the S phase in which they show a pronounced change in radiosensitivity to pnoton injury. These studies are part of the overall goal to research mechanisms of intestinal protection from photon and neutron injury.

UNCLASSIFIED

CONVERSION TABLE

Conversion factors for U.S. Customary to metric (SI) units of measurement.

| TO GET + | BY | | DIVIDE |
|----------|----|-------------|--------|

| angstrom | 1.000 000 X E -10 | meters (m) |
|--|---------------------|--|
| atmosphere (normal) | 1.013 25 X K +2 | kilo pascal (kPa) |
| bar | 1.000 000 X E +2 | kilo pescal (kPa) |
| hern | 1.000 000 X E -28 | meter ² (m ²) |
| British thermal unit | 1.054 350 X E +3 | joule (J) |
| (thermochemical) | | • |
| calorie (thermochemical) | 4.184 000 | joule (J) |
| cal (thermochemical)/cm2 | 4.184 000 X E -2 | mega joule/m ² (MJ/m ²) |
| curie | 3.700 000 X E +1 | gige pecquerel (GBq)* |
| degree (angle) | 1.745 329 X E -2 | radian (rad) |
| degree Fahrenheit | τ =(t°f+459.67)/1.8 | degree kelvin (K) |
| electron volt | 1.602 19 X E -19 | joule (J) |
| | 1.000 000 X E -7 | joule (J) |
| erg | 1.000 000 X E -7 | watt (W) |
| erg/second | 3.048 000 X E -1 | meter (m) |
| foot | 1.355 818 | joule (J) |
| foot-pound-force | 3.785 412 X E -3 | meter ³ (m ³) |
| gallon (U.S. liquid) | 2.540 000 X 3 -2 | meter (m) |
| inch | 1.000 000 X E +9 | joule (J) |
| jerk | 1.000 000 X 2 49 | Gray (Gy)** |
| joule/kilogram (J/kg) (radiation dose absorbed) | 1.000 000 | |
| kilotons | 4.183 | terajoules |
| kip (1000 lbf) | 4.448 222 X E +3 | newton (N) |
| kip/inch ² (ksi) | 6.894 757 X E +3 | kilo pascal (kPa) |
| ktap | 1.000 000 X E +2 | newton-second/m ² (K-s/m ²) |
| micros | 1.000 000 X E -6 | meter (m) |
| sil | 2.540 000 X E -5 | meter (m) |
| mile (international) | 1.609 344 X E +3 | meter (m) |
| ounce | 2.834 952 X E -2 | kilogram (kg) |
| pound-force (lbf avoirdupois) | 4.448 222 | newton (N) |
| pound-force inch | 1.129 848 X E -1 | newton-meter (N·m) |
| pound-force/inch | 1.751 268 X E +2 | newton/meter (N/m) |
| round-force/foot ² | 4.788 026 X E -2 | kilo pascal (kPa) |
| pound-force/inch ² (psi) | 6.894 757 | kilo pascal (kPa) |
| pound-mass (lbm avoirdupois) | 4.535 924 X E -1 | kilogram (kg) |
| pound-mass-foot2 | 4.214 011 X E -2 | kilogram-meter2 |
| (moment of inertia) | | (kg·m²) |
| pound-mass/foot3 | 1.601 846 X E +1 | kilogram/meter ³ |
| pound_mass/100c | | (kg/m ³) |
| rad (radiation dose absorbed) | 1.000 000 X E -2 | Gray (Gy)** |
| | 2.579 760 X E -4 | coulomb/kilogram |
| roentgen | | (C/kg) |
| shaka | 1.000 000 X E -8 | second (s) |
| slug | 1.459 390 X E +1 | kilogram (kg) |
| torr (mm Hg, 0°C) | 1.333 22 X E -1 | kilo pascal (kPa) |

^{*} The becquerel (Bq) is the SI unit of radioactivity; ! Bq = I event/s. **The Gray (Gy) is the SI unit of absorbed radiation.

TABLE OF CONTESTS

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SECTION 1

INTRODUCTION

The intestinal cell renewal system in mammals is one of the most radiosensitive systems in the body and constitutes a doselimiting organ. Animals and man exposed to whole body radiation doses above 15 Gy photons or about 5 Gy fission spectrum neutrons die from a complicated gastrointestinal syndrome associated with diarrhea, malabsorption, bacterial sepsis and the of intestinal stem cell reproductive integrity which leads to mucosal collapse (1). The actual cause of death of the organism has not been associated with any one specific effect and is most likely a response to the perturbation of tissue function associated with the collapse of structural integrity. In turn, the structural integrity of the tissue after radiation is dependent, to a large degree, on the survival and proliferation of thuse cells which reproduce their own intestinal stem cells; population and give rise eventually to the differentiated absorptive villus columnar epithelium. The survival of intestinal stem cells from radiation and the subsequent proliferation of these cells is the basis of the microcolony assay (2). The basic attendant to this assay are; 1) a single surviving assumptions cell gives rise to a single microcolony, 2) clonogenic (stem) cell survival is independent, that is, the survival of one cell will not enhance or decrease the ability of another cell to survive, (this is an assumption associated with clonogenic assays in general and, at this point, there is no evidence to the contrary), 3) the rapidly cycling cells within the crypt are the stem cells (3-7). Presumptive evidence for the third and perhaps most far-reaching assumption comes from the argument in the original paper by Withers and Elkind (3) describing the assay. The authors suggested that in order for a multicellular epithelial foci to form by 4 days, the surviving cells must proliferate rapidly and therefore, must come from cells having a cell cycle time of about 11-12 hours. This is the cell cycle time of the rapidly cycling crypt cell population (8). A more sophisticated argument that intestinal stem cells are rapidly cycling in the normal animal comes from the split dose experiments. of Masuda et al. (6) who showed that the extrapolation numbers between a single dose survival curve and the split dose curve suggested that there were about 140 stem cells per crypt; value consistent with the rapidly cycling cell population within each crypt.

The interpretation of results gathered up to 1975 suggested that the intestinal cell renewal system was fundamentally different than other cell systems such as the hematopoietic or epidermal steady state systems which have a slowly cycling small stem cell compartment which feeds into a rapidly cycling amplification compartment. In contrast, Potten and Hendry (9) carefully analyzed the kinetics of regeneration of intestinal mucosa after irradiation and argued that mucosal regeneration appeared to come from a small population of stem cells, probably in the base of the crypts, which have the subcellular organization associated with a more primitive undifferentiated cell (10,

These results were the impetus for experiments devised in our laboratory to test the hypothesis that the intestine has a small, slowly cycling stem cell population and that this population is responsible for the regeneration of the mucosa following irradiation. In the initial studies, high specific activity tritiated thymidine (HSA 3HTdR) was given either at 1 hour at both 1 and 17 hours before irradiation with graded doses of ** Co for the microcolony assay (12). Crypt damage from the HSA 3-HTdR was measured be dissecting, squashing, and counting the total number of cells per crypt using the method of Wimber et al. (13). Crypt damage was assayed in some animals at the same time other similarly treated animals were given a microcolony assay dose of 60Co. The HSA 3HTdR reduced crypt cellularity from 250 cells to 140 cells within about 6 hours, however, the cell survival curves were identical. These results suggested that there were few intestinal clonogenic stem cells in the S- phase of the cell cycle and supported the results of Potten et al. (9) showing a separate stem cell population. Further supportive evidence came from experiments using prolonged colcemid treatment to selectively kill rapidly cycling cells in the crypt (12). A summary of the experimental design is shown in Figure 1.

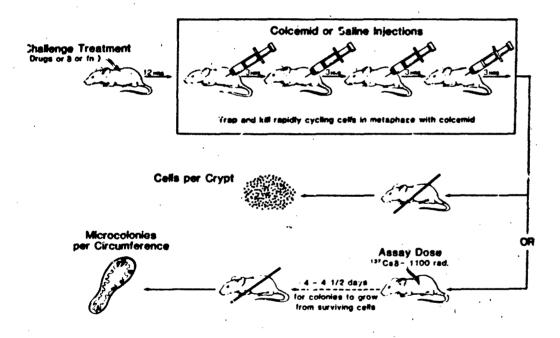


Figure 1. Experimental design of studies using long term colcemid block to selectively kill rapidly cycling cells.

Colcemid, a staphmokinetic agent, prevents the formation of a spindle apparatus and thus prevents anaphase development. Rapidly cycling crypt cells blocked in metaphase began to lyse

after 3 hours. By giving colcemid (150 ug/mouse) every 3 hours for 12 hours (4 IP injections), the crypt cell number was reduced from 250 to about 130. Animals treated with 12 hours of colcemid, however, have clonogenic survival curves identical with control animals having 250 cells per crypt. Prolonged colcemid treatment had no apparent effect on the clonogenic population.

view of our results which have recently been confirmed the proliferative characteristics of the intestinal stem (14),cells that survive radiation is important to investigate. If the stem cells are normally few in number and not in rapid cycle before irradiation; then, the stem cells must be recruited into rapid cycle to produce a large foci of epithelium 4 days later. To determine if radiation could recruit the stem cells into rapid cycle, doses of 0.5 to 2.5 Gy 137Cs were given to mice, whole at 6 hour intervals after this challenge dose of and body, radiation, a 12 hour treatment of colcemid was given. At the end of the colcemid treatment, a single large assay dose of 137Cs was given for the microcolony assay. The experimental design outlined in Figure 1 was used. The results shown in Figure 2 recruitment occurred and the the greatest number of shows that stem cells were killed when colcemid was given beginning 12 hours after the challenge dose of radiation. These results are consistent with the hypothesis that the stem cells are normally few in number and slowly proliferating until recruited into cycle.

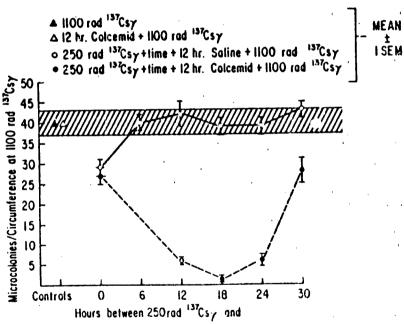


Figure 2. Jejunal microcolonies at a single dose of 11.0 Gy
137Cs in control animals, in animals given 12 hrs colcemid, or in animals given a challenge dose of 2.50 Gy
137Cs before 12 hrs of saline or 12 hrs of colcemid
begun at increasing times after the challenge.

the beginning of 12 hrs. Colcemid or Saline

Radiation is only one of several cytotoxic agents that appears to recruit stem cells from a very slow cycle into a rapid cycle. Our experience has shown that cytotoxic drugs such as Hydroxyurea (HU) (15) and Cytosine Arabinocide (Ara/c) (16) also exert a potent stimulus for intestinal stem cells to enter the cell cycle. Phelps (17) showed that the post Ara/c radiosensitivity of the stem cells was considerably less at 12 hours after Ara/c administration. These results have been confirmed and extended in our laboratory to show that the likely mechanism for the reduced radiosensitivity is an altered proliferative state of the intestinal stem cells. At 12 hours after Ara/c, a portion of stem cells appear to be held up in the less sizable radiosensitive mid to late S portion of the cell cycle. Ara/c is a potent S-phase cytotoxic agent and kills about 90 crypt cells. When Ara/c was followed be 12 hours of colcemid, the total crypt population was reduced to about 80 cells, however, the intestinal stem cells were still radioresistant compared to controls. Therefore, the radioprotection afforded to the intestinal stem cells by Ara/c appears to be through the recruitment of these cells into the more radioresistant mid to late S phase of the cell cycle.

Radioprotection by the thiol compounds are by a different mechanism. The most widely studied and effective IN VIVO radioprotectant among the thiol agents is S-2-'3-aminopropylamino) ethophosphorothioxic acid (WR-2721). The mechanisms of radioprotection of thiol compounds are most likely by hydrogen atom donation, competition of sulfhydryl groups with free radicals (free radical scavenging), or by the induction of hypoxia.

The mechanisms of radioprotection by the two types of agents (recruiting agents and thiol compounds) appeared to be different, therefore studies were undertaken to determine if the combination of these types of agents were additive in their radioprotective effect when given before photons and two types of neutron radiation.

SECTION 2

MATERIALS AND METHODS

Specific Aim 1: To measure clonogenic stem cell survival in control animals and in animals treated with Ara/c, WR-2721, and the combination of both, given before 137Cs gamma-rays, Fermilab neutrons or JANUS neutrons.

Aim la: Radioprotection of intestinal clonogenic stem cells from ^{137}Cs gamma-rays.

Male C3H/HeJ mice (Jackson Laboratories, Bar Harbor, Maine) were housed in the animal quarters at Rush University until they were 100-130 days old. Mice were divided into four main groups; controls (given saline), Ara/c treated (250 mg/Eg), WR-2721 (12 mg/30 g mouse) or the combination of the two agents. The Ara/c treated animals were given graded doses of 127Cs irradiation 12 hours after IP administration of Ara/c, the time which has been shown to yield the greatest radioprotection. The WR-2721 treated animals were similarly irradiated 30 min after IP administration which has been shown to be most effective. In the combination treated animals, the Ara-c was given 12 hours before and the WR-2721 was given 30 min before irradiation. Four days after irradiation, the animals were given 25 uCi tritiated thymidine (3 HTdR) IP and killed 1 hour later. The jejunum was fixed in alcohol, formalin, and acetic acid (AFA, 20:2:1), embedded in paraffin, and sectioned for histology. Autoradiographs were prepared by the dipping technique using Kodak NTB emulsion. The dipped slides containing 5 u cross-sections of jejunum were stored at 4° C for 10 days, then developed in Kodak D-19 developer before they were stained with hematoxylin. After staining, the number of microcolonies were counted per circumference and plotted versus dose of radiation for each of the treatment groups. At the time the animals were killed, a second portion of jejunum was fixed in Carnoy's fixative for the crypt squash preparations as described by Wimber et al. (13).

Aim 1b: Radioprotection of intestinal clonogenic stem cells from Fermilab neutrons.

Male C3H/HeJ mice (100-140 days old) were given Ara/c (250 mg/Kg) or saline and transported to Fermilab so that the animals could be irradiated with neutrons 12 hours later. The neutron beam at Fermilab is produced by a 66.67 MeV proton beam on a "50 MeV" beryllium target with a gold exit face (18). Doses of high energy neutrons (average energy of the farmilab beam is 25 MeV) between 6.5 and 12.0 Gy were given to groups of control mice, mice treated with Ara/c 12 hrs before irradiation, mice treated with WR-2721 one hr before irradiation, and a fourth group treated with the combination of the two agents, Ara/c 12 hrs before and WR-2721 one hr before irradiation. The high energy neutrons were delivered in the following way: unanesthetized animals were placed in perforated tubes held by elastic bands on

a tissue equivalent plastic disk of shonka A-150 material (0.854g/square cm), sufficiently thick for build-up. A second A-150 disk of similar thickness for radiation backscatter was placed such that the mice were sandwiched be the two disks. This assembly was aligned by fixed laser beams which were vertical and perpendicular to the port and 150 cm from the beryllium target. The neutron beam diameter at this distance was about 30 cm with a dose variance of + 3 %. An EXRADIN air-filled ionization chamber, made with Shonka A-150 tissue equivalent plastic walls were used for neutron dosimetry. Neutron flux monitors immediately distal to the target were used to calibrate the bear relative to the ionization chamber measurements. The total Fermilab neutron dose were computer controlled by the flux monitor readings. The neutron doses reported include a gamma component estimated to be about 5-7%. The neutron doses were delivered 12 hrs after Ara/c administration. This time has been shown to produce the maximum protective effect (14,17). WR-2721 was dissolved in phosphate buffered ringers at a pH of 6.8 and given 1 hr before irradiation. IP at a dose of 500 mg/Kg. Sigdestad et al. have shown this dose and time interval to be the most effective (19). After irradiation, the mice were taken back to the Rush-Presbyterian animal facilities and four days later, they were given an IP injection of *HTdR (1 uCi/g body weight) and killed 1 hr Autoradiographs of intestinal cross-sections were examined and the number of microcolonies per circumference were assayed as described and plotted versus Fermilab neutron dose.

 $\lambda im\ 1c.$ Radioprotection of intestinal clonogenic stem cells from JANUS neutrons.

Male C3H/HeJ mice were purchased from Jackson laboratories and sent directly to Argonne National Laboratory. After an appropriate quarantine time, the animals were divided into the same groups as described above: controls, Ara/c given 12 hrs before irradiation, WR-2721 given 1 hr before irradiation, and the combination given at the same times as each agent alone. Irradiations were done by placing the treated mice into plastic cups which were, in turn, placed along isodose lines within the high flux area of the JANUS research reactor (20). The dose rate was 15 cGy per min with a gamma component of about 3%. Four days following irradiation, the mice were injected with 'HTdR and killed one hr later for the microcolony assay as described.

Specific Aim 2: To estimate the LD50/s and LD50/s in controls, Ara/c treated mice, WR-2721 treated mice. and in mice given the combination of the two agents before 137Cs, Fermilab neutrons, or JANUS neutrons.

The same four treatment groups as described above (control, Ara/c 12 hrs before irradiation, WR-2721 one hr before irradiation, or Ara/c 12 hrs before and WR-2721 one hr before irradiation) were used to estimate both the LD50/a associated with intestinal death, and the LD50/s associated with bone marrow death in mice irradiated with 137Cs, Fermilab neutrons, or JANUS neutrons.

The mice irradiated with gamma-rays at Rush were housed in the Rush animal quarters and checked twice daily [LD50/ $_{\circ}$ dose range], or once daily [LD50/ $_{\circ}$ dose range]. The data were collated on the 5th day or the 30th day.

The mice to be irradiated with Fermilab neutrons were ferried to the neutron treatment facility in a car, then returned to the Rush animal facility where they were checked at the appropriate times.

Mice irradiated with JANUS neutrons were housed at Argonne National Laboratory animal facilities where they were kindly checked for mortality by Ms Jane S. Heulsch.

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SECTION 3

RESULTS

Aim 1a: Radioprotection of intestinal clonogenic stem cells from 197Cs gamma-rays.

The clonogenic stem cell survival curve for the control animals was similar to that found previously (12), Figure 3. The De was 1.56 ± 0.13 Gy. At 12 hours following a single injection of Ara/c, the De was similar to the control value (1.64 ± 0.15 Gy); however, the shoulder of the survival curve was increased (figure 3). WR-2721 increased both the shoulder and the slope of the clonogenic survival curve. The De was 1.96 ± 0.19 Gy. The greatest radioprotection was seen when the combination of treatments was given, Figure 3.

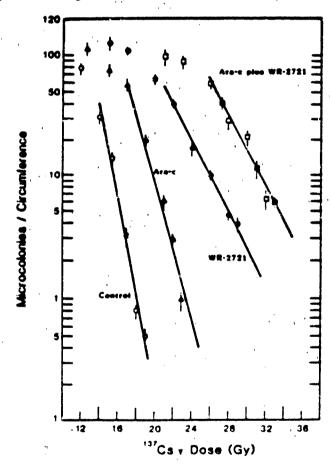


Figure 3. Jejunal microcolonies per circumference in control mice or in mice given Ara/c 12 hours before, WR-2721 1 hour before, or the combination of the two agents; Ara/c 12 hours and WR-2721 1 hour before irradiation with graded doses of 137Cs.

The shoulder was greatly increased; however, the slope remained about the same as in the animals treated with WR-2721 alone. The De in the combination treated animals was 1.87 \pm 0.14 Gy.

The radioprotection shown in the Ara/c treated animals was at a time when there were only about 170 cells remaining out of the normal 250 cells per crypt in untreated animals as shown in Figure 4. This reduction in cells in Ara/c treated animals was consistent with the S-phase cytotoxicity of the drug.

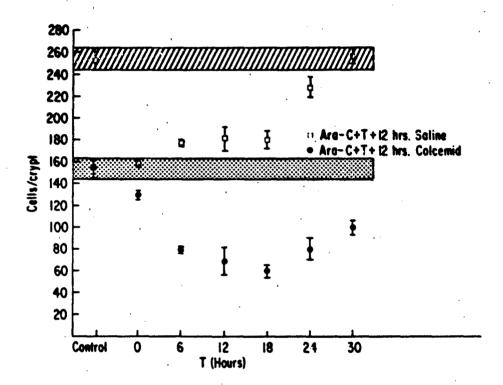


Figure 4. Number of cells per crypt in control (untreated) animals or at various times after Ara/c in animals given 12 hours saline of 12 hours colcemid block.

It is of interest to note that the animals given the colcemid had crypts consisting of only about 70 cells and yet the radiation survival curve showed the same degree of radioprotection as in the animals given Ara/c alone. These data are a strong demonstration that the rapidly cycling cells are not the clonogenic population.

Aim 1b: Radioprotection of intestinal clonogenic stem cells from Fermilab neutrons.

The clonogenic cell survival after Fermilab neutrons is shown in Figure 5.

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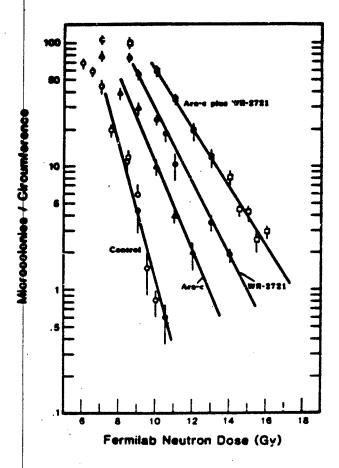


Figure 5. Jejunal microcolonies per circumference in control animals, or in animals treated with Ara/c 12 hours before, WR-2721 one hour before, or the combination; Ara/c 12 hours before and WR-2721 1 hour before graded doses of Fermilab neutrons.

The control curve had a D₀ of 1.05 ± 0.13 Gy. The D₀ was increased at 12 hours after Ara/c; however, the shoulder was the feature of the cell survival curve that was changed the most. The D₀ was increased to 1.27 ± 0.12 . WR-2721 increased the shoulder even more, and the D₀ was increased to 1.35 ± 0.16 Gy. As with the drug-induced changes in the gamma survival curves, the combination of agents altered the curve the most in Fermilab irradiated animals. The shoulder of the curve was extended and the D₀ was increased to 1.54 ± 0.18 Gy.

Aim 1c: Radioprotection of intestinal clonogenic stem cells from JANUS neutrons.

The effect of the high LET, low energy fission spectrum neutrons from the Argonne JANUS reactor on animals given Ara/c and/or WR-2721 in the same regimen as outlined above is shown in Figure 6.

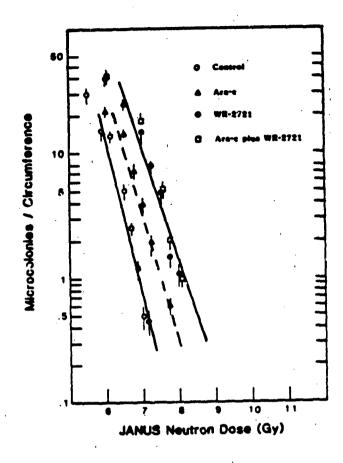


Figure 6. Jejunal microcolonies per circumference in control mice or in mice treated with Ara/c 12 hours before, WR-2721 1 hour before, or the combination of the two agents; Ara/c 12 hours and WR-2721 1 hour before irradiation with graded doses of JANUS neutrons.

The changes were less than those seen for the other types of radiation. The Do for the control animals was 0.53 ± 0.07 . The Ara/c regimen increased the shoulder of the curve; however, the Lo remained about the same at 0.62 ± 0.07 Gy. WR-2721 increased the shoulder but the Do did not change: 0.59 ± 0.09 Gy. The combination of the two agents did not alter clonogenic survival compared to cell survival after WR-2721 alone.

STATES AND STATES AND

Aim 2: The estimate of the LD50/ $_{6}$ and LD50/ $_{30}$ in controls, Ara/c treated mice, WR-2721 treated mice, and in mice given the combination of the two agents before 137 Cs, Fermilab neutrons or JANUS neutrons.

The LD50/s was used to measure mortality in this strain of mice, rather than the more conventional LD50/s since the 6 day time period appears to better reflect death due to the gastrointestinal syndrome. The results of the Ara/c and/or WR-2721 given in the regimens outlined above are shown in Table 1.

Table 1. The mean 137Cs, JANUS neutron, or Fermilab neutron dose (Gray) resulting in 6 day mortality of 50% of a population of C3H/HeJ mice in controls or in mice treated with Ara/c, WR-2721 or the combination of both.

| | LD50/4 | | | |
|------------|-----------------|----------------|----------------|--|
| | 127 Cs | FERMI NEUTRONS | JANUS NEUTRONS | |
| CONTROL | 16.95 | 8.75 | 4.0 | |
| | (16.61-17.28)* | (8.43-9.07) | (3.31-4.69) | |
| Ara/c | 17.6 | 9.21 | 3.9 | |
| | (16.40-17.63) | (8.91-9.5) | (3.24-4.72) | |
| WR-272 | 25.24 | 15.0 | 4.73 | |
| | (25.13-25.34) | (13.52-16.48) | (3.40-5.07) | |
| Ara/c plus | 25.13 | 15.0 | 4.66 | |
| WR-2721 | (24.87-25.39) | (14.26-15.74) | (4.35-4.97) | |
| * 95% Cor | nfidence Limits | | | |

The control LD50/s values for the different radiations were similar to those reported previously (5,7). Ara/c had only a small effect and increased the LD50/s value slightly. WR-2721 had a much greater protective effect, but that effect was greatest for the low LET gamma irradiation as was expected. The protective effect was the least for JANUS neutrons and was intermediate for Fermilab neutrons. The protective factors calculated from Table 1 are given in Table 2.

Table 2. The dose modification (protection) factors for LD50/s calculated from Table 1 for mice treated with the different drug regimens.

PROTECTION FACTORS

LD50/.

| | 137CS | FERMI NEUTRONS | JANUS NEUTRONS |
|-----------------------|-------|----------------|----------------|
| CONTROL | 1.0 | 1.0 | 1.0 |
| Ara/c | 1.04 | 1.05 | 1.0 |
| WR-2721 | 1.5 | 1.7 | 1.2 |
| Ara/c plus WR-2721 | 1.5 | 1.7 | 1.2 |

SECTION 4

DISCUSSION

The most effective exogenous radioprotectants from photon radiation injury in mammals are the thiol compounds developed by the Experimental Therapeutics division at Walter Reed Medical Center (21). The most widely studied and effective IN VIVO radioprotectant among these is WR-2721. The mechanisms of radioprotection of thiol compounds are most likely by hydrogen atom donation (22), competition of sulfhydryl groups with free radicals (free radical scavenging) or by the induction of hypoxia (23). These mechanisms are attributed, in general, to radioprotection by compounds containing thiols, both exogenously administered or endogenous thiol compounds such as glutathione (24,25).

The radioprotection of intestinal clonogenic cells by Ara/c has not been widely studied and the mechanism is unknown. It is particularly interesting that such a potent S-phase cytotoxic agent can protect intestinal stem cells from both photon and neutron irradiation. The most likely explanation is the recruitment of Go stem cells into rapid cycle (26).

It is widely accepted that the stem cells of the bone marrow and the skin are normally in a very long G₁ or in a G₆ stage of the cell cycle out of which a few cells may enter the rapidly cycling pool of cells. After dividing, one of these cells may enter the differentiating amplification compartment and the other may remain a stem cell. Until several years ago, it was believed that the intestinal cell renewal system was fundamentally dif-It was thought that the rapidly cycling cells in the lower two-thirds of the crypt were equivalent to the stem cells, and that by killing these cells with radiation or with cytotoxic drugs, the number of cells which could give rise to the regenerative foci of intestinal epithelial cells to repopulate the mucosa would be recruited. Several experiments in our laboratory showed that this was not true (12,15). Reduction of the rapidly cycling cells in the crypts by about half did not reduce the number of clonogenic cells. These findings were confirmed in the studies reported here. Ara/c reduced the number of cells in the crypt and by 12 hours later, there was less than half the normal number of cells/crypt; yet at this time post-Ara/c treatment, the number of surviving clonogenic cells was greatly increased. These results strongly suggest that the rapidly cycling cells within the crypts are not the clonogenic cells. This same conclusion has now been reached by other investigators (14). This alone does not explain why Ara/c protects intestinal cloncgenic cells from radiation injury. Radioprotection must come from the redistribution of the clonogenic cells within the cell cycle. Specifically, Ara/c must recruit the stem cells into rapid cycle where they are less radiosensitive. At 12 hours after Ara/c, the stem cells must be in mid to late S-phase. The effect of this redistribution on the clonogenic cell survival curve was an increase in the shoulder of the survival curve, but little effect on the slope of the curve. The shoulder of the intestinal survival curve is attributed to repair of sublethal damage (SLD)

and to multiplicity (the number of stem cells per crypt). It has been shown that the multiplicity does not change during the 12 hours after Ara/c (16). These results suggest that increased repair capability may exist in these mid to late S-phase cells. Qualitatively similar results were found in Ara/c treated animals irradiated with the two neutron sources. The least effect of Ara/c was found in animals irradiated with JANUS neutrons and the results from Fermi irradiated animals were intermediate. The reduced cell age effect of neutron irradiation has been documented previously (27).

In contrast to Ara/c, WR-2721 increased both the shoulder and the slope of the intestinal clonogenic cell survival curves. The shoulder was increased for all three types of radiation; however, the slope increase was greater for photon radiation than

for the JANUS neutron radiation.

The effects of the combination of Ara/c at its most protective time interval appeared to be additive when combined with WR-2721 for photon and for Fermilab neutrons. This was not the case for JANUS neutrons where there was no additional effect of Ara/c on the WR-2721 radioprotection. These results could be explained by the reduced effect of cell age distribution on survival after high LET neutron radiation.

In contrast to the effects of Ara/c on clonogenic cell survival, there was little or no effect of this treatment on the LD50/s, nor was there any additive effect when Ara/c was combined with WR-2721. These results suggest that the survival of the intestinal stem cells is not closely associated with the survival The dissociation of animal survival with stem the animal. cell survival was suggested by Lushbaugh (28); however, this view It is also of interest to note that the is not widely held. regimen of Ara/c treatment had no effect on the LD50/30, nor was this regimen additive to WR-2721 changes in the LD50/10, suggesting that the marrow stem cells do not respond or, at least, do not respond within the same time frame; however, data from other laboratories clearly indicate that the CFU-S can be recruited into rapid cycle following cytotoxic drug treatment such as hydroxyurea (29).

it has been shown that the potent S-phase In summary, cytotoxic agent, Ara/c, given 12 hours before both neutron and gamma irradiation protects cells from some degree of injury. This protection is seen at a time when the total number of cells per crypt is reduced to about half the normal number. results strongly suggest that the number of clonogenic cells are few in number and that they are in a G_0 or an extended G_1 stage The most likely mechanism for the observed of the cell cycle. Ara/c induced radioprotection is through the redistribution of clonogenic cells mainly into the mid to late S-phase of the cell cycle. This radioprotection is additive to the protection by WR-2721 for low LET irradiation but little or no additivity was seen when combined with WR-2721 before high LET radiation. In spite of the radioprotection in intestinal stem cells, there was no effect of Ara/c on the LD50/6 with or without WR-2721 (irrespective of the radiation source) suggesting the dissociation of stem cell survival from animal survival over the short term; however, long term survival must depend upon the survival of the stem cells.

SECTION 5

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